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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,454	03/22/2005	Augustinus Bader	LORWER P33AUS	7961

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,454	BADER, AUGUSTINUS	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-123* is/are pending in the application.

4a) Of the above claim(s) *100-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-95 and 97-99* is/are rejected.

7)☒ Claim(s) *87 and 96* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants reply of 25 June 2007 has been received and entered into the application file. Claims 87, 94, 96 and 98 have been amended; new claims 113-123 have been added; claims 1-86 were previously cancelled. Claims 87-123 are pending in the current application, of which claims 100-112 have been withdrawn from consideration as being directed to non-elected inventions. Claims 87-99 and 113-123 have been considered on the merits.

Claim Objections

The following informalities persist in the instant claim set:

In claim 87, the 11th line (step (d)) should read, "...cells in said porous support structure;..." It appears Applicants intended to delete the word "to" as suggested; however to delete a word less than five letters double brackets must be used. The single brackets around the word "the" will not result in the word being deleted from any resulting patent. Correction is required.

In claim 96, in line 9 (step (d)) "cells" is still misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 87-95 and 97-99 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 87, step (e) remains indefinite, as it is still not clear when the boundary layer is removed, it appears "after completion of the cell-formation process" refers to the cell growth period recited in step

(d); however, there is technically no antecedent basis for the limitation "the cell-formation process" as recited in step (e). Applicants must amend the language to clearly define when the boundary layer is removed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicants have argued that the method and device of Bader (WO 01/09282) (hereafter Bader' 282) are distinct from the method currently claimed, and that the method of Bader '282 actually teaches away from the instant method. Specifically, Applicant argue that the current amendments to the claims require the boundary layer material to 'substantially conform in size and shape' to the porous support structure, which they argue is not taught by Bader '282. Applicants further argue that the method of Bader '282 does not permit formation of the support structure into a predetermined shape *prior* to insertion into the culture chamber, but rather Bader '282 defines the shape and size of the culture chamber by means of the carrier plate and cover plate, only after formation of the cell culture chamber is the extracellular matrix inserted within the cell culture chamber. Therefore Applicants are arguing that the method of Bader '282 does not follow the sequence or steps of the instant claims, which require the boundary layer to be applied to the support structure. Still further, Applicants argue that the size and shape of the body part to be replaced is determined by the size and shape of the carrier plate, not the extracellular matrix material which is inserted. Applicants also argue that Bader '282 specifically teaches away from the sequence of steps in the instant invention, because Bader '282 describes embodiments

wherein cells and collagen (the extracellular matrix material) are injected simultaneously, which would prevent the ECM from being "preformed into a predetermined shape".

In response to Applicants' argument that the films (boundary layer) of Bader '282 do not substantially conform in size and shape to the extracellular matrix (porous support structure), it is respectfully submitted that the requirement that the boundary layer only 'substantially conform' in size and shape does not serve to differentiate from the disclosure of Bader '282. The term "substantially" is a relative term of degree which is not clearly defined in the specification, and therefore is given its broadest reasonable interpretation. Because the films of Bader '282 are of appropriate size and shape to encompass and cover the extracellular matrix material, they are considered to at least 'substantially conform to the size and shape' of the extracellular matrix material. Clearly if they did not at least substantially conform, the extracellular matrix material would not be able to fit within the cavity formed between the films.

In response to Applicants' argument that the method of Bader '282 involves first forming the cell culture chamber by configuring the cell carrier plate and cover plate into a predetermined shape, and subsequently inserting the extracellular matrix, as opposed to the instant method which requires application of the boundary layer material to the support structure, it is respectfully submitted that Applicants are reading Bader '282 too narrowly. It appears Applicants are submitting that because Bader '282 inserts the extracellular matrix into a cell culture chamber which is defined in shape and size by the carrier and cover plates, the extracellular matrix material cannot be preformed, but would rather be injected and then take the form of the cell culture chamber. However, this is not considered accurate; Bader '282 is not limited to embodiments wherein ECM material, such as fluidized collagen, is injected into the cell culture chamber to fill the full volume of the cell culture chamber. Bader '282 further describes that the extracellular matrix material may alternatively consist of bone-like material, or

calcareous material, such as tricalcium phosphate; clearly such ECM materials would not be injected, but would be preformed into a desired shape or structure, and then inserted (as opposed to injected) into the cell culture chamber. It is further submitted that there is nothing in the instant independent claims, or any claims under rejection under 35 USC 103(a) that requires the boundary layer material to be *applied* to the porous support structure, rather the instant claims under rejection only require encapsulation of the entire support structure. Therefore, inserting the extracellular matrix into the cell culture chamber formed between the films in Bader '282 does read on the method of the claims under rejection.

Regarding Applicants' argument that the size and shape of the construct formed is determined by the size and shape of the carrier plate, not the predetermined size and shape of the ECM material, it is again submitted that this is too narrow a reading of Bader '282. Wherein materials such as tricalcium phosphate are used as the ECM, the ECM would have a predetermined shape prior to insertion into the cell culture chamber. It is noted that the limitation requiring the support structure to correspond to a body part is non-limiting as to what body part; therefore, the support structure may conform to any whole organ or tissue fragment thereof (for example, bone fragments which may be used to fill a specific sized void or defect). Therefore, any shape of ECM can be considered 'preformed' to 'correspond' in size and shape to some body part.

Finally, in response to Applicants' argument that Bader '282 teaches away from the instant invention because they disclose embodiments wherein cells are injected via inflow and outflow lines simultaneously with collagen (ECM material), it is submitted that the teachings of Bader '282 are being construed too narrowly. The fact that Bader '282 provides inflow and outflow lines, and suggests that cells and/or ECM material may be delivered via these routes cannot be relied upon to that cells cannot be delivered via these inflow lines in situations where a preformed ECM (such as tricalcium phosphate) has previously been inserted into the cell culture chamber.

Claims 87-90, 92 and 94 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bader (WO 01/09282) (translation provided for US national stage application 10/048,440 replied upon for English version- pages cited are those of application 10/048,440).

Bader teaches a cell culturing device and a method of culturing cells on said device to produce a tissue construct which can be in a desired shape. The cell culture device of Bader comprises a support, such as a cell carrier plate; a carrier film laid directly on the support; and a flexible plastic cell-culture film that is attached at the edges to the carrier plate and/or carrier film so as to form a cell culture chamber between the two films (See Bader, abstract). The cells may be cultured directly in the cell culture chamber on the films or an extracellular matrix may be placed in the interior of the cell culture chamber to provide a substrate for the cells (See Bader, Pg. 11, ln 7-19).

In comparing the method of Bader (WO 01/09282) to the instant invention, the extracellular matrix is considered to read on the 'porous support structure'; the films are considered to read on the 'boundary layer' which surrounds the extracellular matrix (porous support structure). The extracellular matrix (porous support structure) can comprise collagen (See Bader, Pg. 14, ln 26-36) or tricalcium phosphate (See Bader, Pg. 11, ln 14-19), both are porous materials which are permeable to the cells and can be degraded or absorbed by the cells (which applicant calls biologically converting the support structure). The cell carrier and/or cell culture films (boundary layer) may be gas-permeable (See Bader, abstract); furthermore because the films form the cell culture chamber, both films (which make up the boundary layer) must be impermeable to cells so as to retain the cell culture in the defined area. The films (boundary layer) may consist of PTFE, silicone, polylactide, polyhydroxyalkanoate, or polyhydroxidebutyrates (See Bader, Pg. 18, ln 24-30); such materials are synthetically made from biological materials, thus they are considered both 'synthetic' and 'biological' materials.

The method of cell culture disclosed by Bader (WO 01/09282) comprises introducing cells into the extracellular matrix (porous support structure) which is located within the cell culture chamber formed

by the films (boundary layers), and supplying nutrients to the cells on the extracellular matrix (porous support structure) via inflow and outflow lines; oxygen is supplied to the growing cells through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27).

In order to more clearly show how the method of Bader reads on the instantly claimed method, each of the claimed steps will be further discussed below:

Regarding the step of forming the inert porous support material into the desired shape, it is noted that Bader teaches the extracellular matrix (porous support structure) can approximate the size and shape of a desired tissue, for example, bone, heart valve or bladder, so that the finished cell culture may be used to reconstruct the desired tissue (See Bader, Pg. 14, ln 9-17); thus it is inherently required that an initial step comprise forming the extracellular matrix material into the desired shape and size. It is further noted that the extracellular matrix material, once formed, at least 'substantially maintains' the predetermined shape.

Regarding the step of encapsulating the entire porous structure by means of a boundary layer of cell-impermeable material, it is noted that Bader teaches the cells are introduced into the extracellular matrix (porous support structure) inside the cell culture chamber (which is formed by the films (boundary layers)); therefore, the extracellular matrix (support structure) is placed within the cell culture chamber formed by the films (boundary layer), and thus the extracellular matrix is encapsulated by the films (boundary layer). Because the films encompass the extracellular matrix, they are considered to 'substantially conform' to the predetermined size and shape of the extracellular matrix material. Please note the claims must be given their broadest reasonable interpretation. The new limitation that the boundary layer must 'substantially conform in size and shape to the porous support' is not clearly defined in the specification; therefore in giving this limitation ("substantially") its broadest reasonable interpretation, any correlation between the films (boundary layer) and the extracellular matrix (porous

support structure) is considered to read on the instant limitations. Furthermore, the fact that the extracellular matrix material fits within the films (boundary layer) means there must be some substantial correlation in shape and size, as they are compatible with one another, clearly two objects which have no correlation in size and shape would not be able to be combined, one within the other.

Regarding the step of introducing the cells to the porous support structure, it is noted that Bader teaches inoculating the cells onto the extracellular matrix (porous support material) via inflow and outflow lines (which applicants call inlets) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27).

Regarding the step of promoting cell growth by introducing oxygen and nutrients into the porous structure and allowing cells to consume the nutrients and the oxygen and to grow and conform to the shape and size of the porous support structure, it is noted that Bader teach nutrients is supplied to the cells on the extracellular matrix (porous support structure) via the inflow and outflow lines and oxygen is supplied to the growing cells through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27). Furthermore, it is noted that the nutrient medium is considered to read on the 'intermediate layer', and thus supplying the nutrient media via the inflow and outflow lines is considered to read on the step of supplying an intermediate layer.

Finally, regarding the step of removing the boundary layers, it is noted that Bader teaches the films (boundary layers) are removable, or may be dissolvable, after the cell culture is complete (See Bader, Pg. 14, ln 14-21); however, they do not specifically teach removing the films, and thus differs in this point.

However, it would have been obvious to one of ordinary skill in the art to remove the films (boundary layers) after the cell culture is complete in order to recover and use the tissue construct produced, which has the shape originally provided by the extracellular matrix (porous support structure). One would expect success in removing the films (boundary layer) in order to recover the tissue construct because Bader teaches the films (boundary layer) are removable or dissolvable (Claims 87-90, 92 and 94).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 96 and dependents thereof would be allowable if the cause of objection to claim 96 is corrected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651